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(71) Applicant *(for all designated States except US)*: **GALEPHAR M/F** [BE/BE]; Rue du Parc Industriel 39, B-6900 Marche-en-Famenne (BE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VANDERBIST, Francis** [BE/BE]; Avenue des Jardinets 18, B-1170 Bruxelles (BE). **SERENO, Antonio** [BE/BE]; Passiewijk 21, B-1820 Melsbroek (BE). **BAUDIER, Philippe** [BE/BE]; Rue Engeland 338, B-1180 Uccle (BE).

(74) Agents: **POWIS DE TENBOSSCHE, Roland** et al.; Cabinet Bede S.A., Place de l'Alma 3, B-1200 Brussels (BE).

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WO 02/32427 A1

(54) Title: STABLE ORAL FORMULATION CONTAINING BENZIMIDAZOLE DERIVATIVE

(57) Abstract: An enteric formulation containing at least one benzimidazole derivative, said formulation comprising: a core containing at least one benzimidazole derivative and at least one lipophilic antioxidant, and an enteric envelope protecting the core at least at a pH of 3 to 5, preferably at a pH of 1 to 5.

STABLE ORAL FORMULATION CONTAINING BENZIMIDAZOLE DERIVATIVE

Field of the invention

The present invention relates to a stable, pharmaceutically acceptable oral dosage form of a benzimidazole derivative as well as to an advantageous and economical process for manufacturing the same.

Description of the background

Omeprazole or 5-methoxy-2 (((4-methoxy-3,5-dimethyl-2-pyridinyl) methyl)sulfinyl)-1H-benzimidazole is a useful and very widely used treatment of gastric and duodenal ulcer, erosive esophagitis and gastroesophagal reflux disease. Omeprazole acts by inhibiting gastric acid secretion. The usual daily dosage is from 10 to 100 mg of omeprazole in one dose.

The formulation of omeprazole must be protected from gastric fluids since it is rapidly chemically degraded at acidic pH. Consequently, omeprazole is usually released in the proximal parts of the small intestine where it is rapidly absorbed. The absolute bioavailability of omeprazole with doses of 20 to 40 mg/day is approximately 30% to 40%.

Different oral compositions of omeprazole have been described in the past. The US patent 4786505 describes a pharmaceutical preparation containing an acid labile compound together with an alkaline reacting compound and together with an alkaline compound as the core material. This patent also described one or more subcoating layers and an enteric coating as well as a process for the preparation thereof.

The US Patent 5232706 is quite close to the one mentioned hereinabove. It describes a preparation comprising a nucleus formed by a mixture of omeprazole with a basic compound. The nucleus has two coatings. The first is formed by an enteric coating.

The US Patent 5385739 relates to a stable formulation of omeprazole microgranules containing a neutral core consisting of sugar and starch, characterized in that it contains an active layer consisting of a dilution of omeprazole in mannitol in substantially equal amounts. It also relates to a process for producing such formulations.

The US Patent 5690960 relates to a new oral pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole, a method for the manufacture of such a formulation.

Finally, the US Patent 5817338 describes a new pharmaceutical multiple unit tabletted dosage form containing omeprazole, a method for the manufacture of such formulation, and the use of such formulation in medicine.

Omeprazole degrades very rapidly in water solutions at low pH values. The rate of degradation proceeds with a half-life of less than 10 minutes at pH values below 4. At pH 6.5, the half-life of degradation is 18 hours; at pH 11 about 300 days. But omeprazole is susceptible to degradation not only in an acidic environment but also under the influence of temperature, humidity, organic solvents and oxygen. Degradation of omeprazole is known to give decomposition products that are highly colored. Consequently, inappropriate conditions of handling of the product will cause discoloration even at small levels of degradations.

The galenic formulation and the manufacturing process should therefore be carefully optimized to guarantee the stability of the composition through the entire shelf-life of the drug medicine.

Brief description of the invention

An object of the present invention is to provide a stable oral composition of a benzimidazole derivative and a process thereof. The new dosage form is characterized as follows: the benzimidazole derivative is formulated in the form of an enteric coated tablet. The core tablet contains at least, in addition to the active ingredient, one lipophilic antioxidant agent. An isolating coating layer is applied on the core tablets before the enteric coating.

The invention relates thus to an enteric formulation containing at least one benzimidazole derivative, said formulation comprising:

- a core containing at least one benzimidazole derivative and at least one lipophilic antioxidant, and
- an enteric envelope protecting the core at least at a pH of 3 to 5, preferably at a pH of 1 to 5.

For example, the enteric envelope protects the benzimidazole derivative in such a way that the half-life of benzimidazole derivative in a water bath having a temperature of 37°C and a pH comprised between 3 and 5 is greater than 30 minutes, advantageously greater than 1 hour, preferably greater than 2 hours, most preferably greater than 4 hours or even more, such as 5 hours, 6 hours, 7 hours, 10 hours, 20 hours.

The core is advantageously selected from the group consisting of tablets and granules, for example a mixture of particles with a size of less than 3mm, such as a size of less than 1mm.

Preferably, the invention relates to an enteric coated tablet or granule containing at least one benzimidazole derivative, and most preferably an enteric coated tablet containing at least one benzimidazole derivative. The tablet or granule of the invention comprises a core containing at least one benzimidazole derivative and at

least one lipophilic antioxidant, said core being provided with at least one enteric coating layer.

According to a preferred embodiment, the tablet or granule of the invention comprises:

- a core containing at least said benzimidazole derivative and at least one lipophilic antioxidant;
- an enteric coating layer, and
- a pre-coating layer or isolating layer extending between the core and the enteric coating layer.

Advantageously, the core comprises at least a tabletting excipient on which at least a part of the lipophilic antioxidant is attached. Preferably, substantially all the tabletting excipient(s) is(are) provided with lipophilic antioxidant, while most preferably substantially all the lipophilic antioxidant is attached to the tabletting excipient.

For example, at least a part of the lipophilic antioxidant is adsorbed on a tabletting agent or granulated with a tabletting agent.

According to advantageous detail, the core comprises tabletting excipient or tabletting particles covered with a layer containing at least one lipophilic antioxidant.

Preferably, the enteric coating or envelope is substantially free of benzimidazole derivative, and is most preferably free of benzimidazole derivative. Such a coating can be obtained for example on a tablet or granules by using a pre-coating layer or an isolating layer.

The pre-coating layer or isolating layer is also advantageously substantially free of benzimidazole derivative.

According to a detail of an embodiment, the core comprises at least a tabletting excipient selected among the group consisting of microcrystalline cellulose, cellulose derivatives, lactose, mannitol, mono or disaccharide, and mixtures thereof, on which at least one lipophilic antioxidant is attached. Preferably, substantially all the tabletting excipient(s) is (are) selected from said group.

Advantageously, at least one lipophilic antioxidant agent is selected from the group consisting of derivatives of vitamin E (α-tocopherol) and mixtures thereof. Preferably, substantially all the lipophilic antioxidant agent(s) present in the core is (are) selected from said group.

Preferably, the lipophilic antioxidant comprises at least vitamin E polyethylene glycol succinate (Vitamin E TPGS) and is most preferably vitamin E polyethylene glycol succinate (Vitamin E TPGS).

The pre-coating layer or the isolating layer comprises advantageously at least a polymer selected from the group consisting of povidone, derivatives of povidone, derivatives of cellulose, and mixtures thereof. Preferably, said polymer(s) forms at least 50% by weight (most preferably at least 75% by weight, for example substantially completely) of the dry pre-coating layer or isolating layer (water-solvent free).

The enteric layer or envelope comprises advantageously at least one cellulosic polymer or cellulosic derivative. Preferably, the enteric layer or envelope comprises from 20 to 70% by weight (most preferably from 30 to 60% by weight, especially about 50% by weight) of cellulosic polymer and cellulosic derivative.

According to a preferred embodiment, the enteric layer or envelope comprises at least hypromellose phthalate as cellulosic derivative and/or at least an acrylic/methacrylic polymer or copolymer, preferably a methacrylic acid copolymer.

The benzimidazole derivative is advantageously selected from the group consisting of benzimidazole derivatives inhibiting the proton pump, pantoprazole, lansoprazole, omeprazole and mixtures thereof. According to a specific embodiment, the benzimidazole derivative is omeprazole.

The invention relates also to a capsule containing granules containing the benzimidazole derivative and a lipophilic antioxidant, the capsule being an enteric

capsule, i.e. a capsule which degrades or which is soluble at pH>5 and which is not degraded at pH comprised between 1 and 5, or a common capsule in case the granules are protected with an enteric coating.

According to a possible embodiment, the tablet of the invention or the capsule of the invention contains from 5 to 80 mg omeprazole.

The invention relates also to a process for the preparation of a formulation of the invention, in which the core is prepared from a mixture comprising a tabletting excipient on which a lipophilic antioxidant is attached and a benzimidazole derivative, and in which the core (for example in the form of a tablet or granules) is provided with at least an enteric layer or envelope.
Advantageously, the tabletting excipient on which a lipophilic antioxidant is attached is prepared by mixing the lipophilic antioxidant in molten phase with tabletting excipient.
Preferably, the core of the formulation is manufactured by direct compression.
The core has advantageously the form of a tablet or granules, which is/are provided with an enteric coating or with a pre-coating by using the pan-coating technology or the fluid bed technology.

Brief description of the drawing

Figure 1 gives the dissolution profiles of omeprazole formulation of the invention (tablet SMB 20 mg), as well as of marketed omeprazole formulations.

Description of examples of the invention

A preferred embodiment of the invention is a stable formulation of omeprazole or of another benzimidazole derivative under the form of a pharmaceutical coated tablet.

The tablet comprises a core which contains, in addition to several excipients used in the manufacturing of pharmaceutical tablets, an adsorbate (or granulate) of a lipophilic antioxidant derivative on a cellulosic derivative.

This adsorbate is mixed with the active ingredient and the tabletting excipients. The whole blend is tabletted by a direct compression process.

The adsorbate mentioned hereinabove is formed by melting the lipophilic antioxidant derivative and adding it in the liquid form to a classical tabletting excipient in a planetary mixer. The antioxidant derivative solidifies when put in contact with the tabletting excipient.

It has been found that by using the lipophilic antioxidant, in the form of the antioxidant adsorbate in the preferred examples, it was possible to prepare formulation having an excellent stability. The core of the tablet so manufactured is coated as follows: first with an isolating layer and then with an enteric coating layer.

The direct coating of the tablets with the enteric layer was prevented in the preferred example, so as to avoid possible degradation of the active ingredient due to the presence of acidic groups in the enteric polymer. Therefore, a neutral coating layer is advantageously applied on the core tablets before the application of the enteric coating.

The isolating coating layer of these examples contains at least one water soluble polymer as, for example, povidone or hypromellose. Povidone is the preferred excipient for the isolating layer because this polymer is soluble in absolute alcohol while the cellulosic derivatives need traces of water to be completely soluble. And it

is well known that the presence of water, even in traces, is able to accelerate/provoke a chemical degradation of benzimidazole derivatives.

The enteric coating polymer may be a derivative of cellulose (cellulose acetophthalate, hypromellose phthalate) or a derivative of an acrylic polymer (methacrylate acid copolymer).

The preferred enteric polymer must be able to protect the formulation at acidic pH corresponding to the transit in the stomach (pH comprised between 1 and 5) and to release the active ingredient rapidly once the formulation arrives in small intestine. Therefore, hypromellose phthalate (HP50®, Shinetzu) is the preferred polymer for this purpose since it has the properties to be soluble at pH>5.0.

Several formulations for the core of the example of tablets, the isolating coating layer and the enteric coating layer are given hereinbelow:

FORMULATIONS A to D:

The formulations A to D comprise a core (Ometab), provided with a pre-coating and with an outer enteric coating. The compositions of the core, pre-coating and enteric coating for the different formulations is given in the following tables.

Composition of the core - Ometab (mg) of the formulations A to D

Formulation Composition in mg of the core	A	B	C	D
OMEPRAZOLE	10	10	10	10
Vitamine E TPGS	10			
Microcrystalline Cellulose	16.6	16.6	16.6	

Crospovidone	8.5	8.5		
Lactose	104	114		114
Mannitol			122.5	25.1
Mg stearate	1	1	1	1

Coating isolation or pre-coating (mg of dry matter applied on a tablet)

Formulation Composition in mg of the pre-coating	A	B	C	D
Povidone	7.5		15	
HPMC		7.5		10

HPMC : hydroxy propyl methyl cellulose

The pre-coating was applied by using a solution of Povidone or HPMC, said solution containing preferably absolute ethanol as solvent or an hydro-ethanolic mixture.

Enteric coating (mg of dry matter applied on a tablet)

Formulation Composition mg of the enteric coating	A	B	C	D
Eudragit (Methacrylic Acid Copolymer) L 30D - 55			7.3 (dry)	7.3 (dry)
HP 50 (Hydroxypropyl Methylcellulose phthalate	7.3	7.3		
Talc	4.445	4.445	4.445	4.445
Povidone			1.818	1.818
Triacetine	1.836			
Triethyl citrate			1.836	
Diethyl phthalate		1.836		
Polyethylene glycol				1.836
Red iron oxide	1.43	1.43	1.43	1.43

The enteric coating was applied by using a solution containing the different compounds listed in the above table, and a hydro-ethanolic mixture, the weight ratio compounds listed in the table/ hydro-ethanolic mixture being 15/85.

The excellent stability of omeprazole formulation of the invention containing a lipophilic antioxidant agent was demonstrated by comparing the stability of enteric coated tablets with and without an antioxidant agent.

For said tests, three tablets were formulated as follows:

Tablets 1, 2 and 3

Core of tablet (mg per tablet)	1	2	3
OMEPRAZOLE	10	10	10
Vitamin E	0	10	0
Vitamin E TPGS	10	0	0
Microcrystalline cellulose	16.60	16.60	16.60
Crospovidone	8.50	8.50	8.50
Monohydrate lactose	104	104	104
Magnesium stearate	1.00	1.00	1.00

Pre-coating

Pre-coating of tablet (per tablet, mg)	1	2	3
POVIDONE	6.10	6.10	6.10

Enteric coating composition

Enteric coating of tablet (per tablet, mg)	1	2	3
Hypromellose phthalate	5.60	5.60	5.60
Talc	3.40	3.40	3.40
Glycerol triacetate	2.80	2.80	2.80

After storing for 1 month the 3 compositions at 40°C/75% Relative humidity, the following observations have been made.

The formulation 3, i.e. the tablet containing no antioxidant agent showed a clear instability. Indeed, the tablet developed an intense violet coloration (characteristic to a degradation of omeprazole).

The formulation 2, i.e. the tablet containing α-tocopherol as antioxidant agent, was stable since after 1 month of storage, only a slight yellow coloration appeared on the tablet.

The formulation 1, i.e. the tablet containing Vitamin E polyethylene glycol succinate (Vitamin E TPGS) as antioxidant agent, had a better stability than that of formulation 2, since the tablet was still completely white after 1 month of storage at 40°C/75% Relative humidity.

For showing the usefulness of the isolating coating layer, the stability of a formulation (formulation 4) containing no pre-coating was compared to the stability of formulation 1. The core and the enteric coating of formulation 4 correspond to the core and the enteric coating of formulation 1, i.e. formulation 4 differs from formulation 1 by the absence of the pre-coating.

The formulation 1 containing the pre-coating layer has given a product white at the end of the manufacturing process, while the formulation 4 shows the apparition of violet spots on the omeprazole tablets. It is thought that the violet spots are due to (i) the acidic groups contained in the enteric coating layer which are able to react with omeprazole on the surface of the tablet and/or (ii) to the water contained in the enteric coating solution, said water being able to provoke and/or accelerate the degradation of omeprazole present on the surface of the tablet.

Therefore, it is thought that the isolating layer is useful in the present invention for protecting the omeprazole molecules located at the surface of the core tablets. The coating suspension or solution used for said pre-coating contains preferably no water (use of absolute alcohol as solvent for preparing the coating solution or suspension).

Hereinbelow is described an example of manufacturing process of a formulation of the invention, in the form of enteric coated tablets.

STEP 0

Control of the cleanliness of premises, material and equipment

STEP 1 : Weighing

Individual weighing of raw materials

STEP 2 : Pre-Blending

Equipment

Planetary mixer

Operation

Vitamin E TPGS is heated until it becomes liquid. It is then adsorbed onto Microcrystalline Cellulose by a mixing operation.

STEP 3: Blending

Equipment

Planetary mixer

Operation

Introduce in the mixer the adsorbed vit.E TPGS, crospovidone, lactose, magnesium stearate and omeprazole.

Homogenise.

STEP 4: Tabletting

Equipment

Automatic tabletting machine type Courtoy

Operation

Adjust the parameters. Proceed to the direct compression of the powder.

STEP 5: Preparation of pre-coating solution

Equipment

High shear mixer

Operation

Prepare the pre-coating solution by dissolving povidone into anhydrous ethanol.

STEP 6: Pre-Coating

Equipment

Pan coating type Pelligrini

Operation

The tablets are coated

STEP 7: Preparation of Enteric coating suspension or solution

Equipment

High shear mixer

Operation

Prepare the coating suspension by suspending Hypromellose phthalate in a mixture ethanol-water.

Stirring constantly with a high shear mixer equipment and add triacetin, talc and red iron oxide. Homogenize.

STEP 8: Coating

Equipment

Pan coating type Pelligrini

Operation

The tablets are coated

STEP 9: Drying

Dry coated tablets

STEP 10: Packaging

A part of the tablets is packaged in alu-alu blisters (stability studies).

Another part is packaged in HDPE bottles (stability studies and clinical trials).

Another possible advantage of the tablets of the present invention is the low cost of the manufacturing process, in comparison to the existing marketed compositions of omeprazole (pellets, multi-units tablets).

A disintegration test has been performed to prove that the enteric coating was able to protect the composition at pH=1 for 2 hours. This test has been performed as described in E.P. 3rd edition, 2.9.1. The test has been performed on three consecutive pilot batches (24G00/A, 24/G00/B, 24G00/C). The results were conform to the specification for each batch since absolutely no disintegration appears on any tablets after 2 hours at pH=1.

The dissolution test has also been performed on the batch 24G00/B and meets the specification (NL more than 80% of omeprazole dissolved 60 minutes after starting the dissolution test). The dissolution profile of the enteric coated tablets described in this invention has been compared with the dissolution profile of various marketed forms of omeprazole: LOSEC 20 mg (Astra, Belgium), MOPRAL 20 mg (Astra, France), ANTRA MUPS 20 mg (Astra, Germany). Figure 1 gives the comparative dissolution profiles of omeprazole formulation of the invention (tablet SMB 20 mg), as well as of marketed formulations (Antra, Mopral and Losec).
It can be observed that the in vitro dissolution rates of marketed pellets and of the formulation of the present invention are similar.

What we claim is:

1. An enteric formulation containing at least one benzimidazole derivative, said formulation comprising:
   - a core containing at least one benzimidazole derivative and at least one lipophilic antioxidant, and
   - an enteric envelope protecting the core at least at a pH of 3 to 5, preferably at a pH of 1 to 5.
2. The formulation of claim 1, in which the core is selected from the group consisting of tablets and granules.
3. The formulation of claim 2, in which the core is selected from the group consisting of tablets and granules, said tablets or granules being provided with at least one enteric coating layer forming an enteric envelope.
4. The formulation of anyone of the claims 1 to 3, which comprises a tablet or granules comprising at least:
   - a core containing at least said benzimidazole derivative and at least one lipophilic antioxidant;
   - an enteric coating layer, and
   - a pre-coating layer or isolating layer extending between the core and the enteric coating layer.
5. The formulation of anyone of the claims 1 to 4, in which the core comprises at least a tabletting excipient on which at least a part of the lipophilic antioxidant is attached.
6. The formulation of claim 5, in which at least a part of the lipophilic antioxidant is adsorbed on a tabletting agent or granulated with a tabletting agent.
7. The formulation of claim 5, in which the core comprises tabletting exipient covered with a layer containing at least one lipophilic antioxidant.

8. The formulation of anyone of the claims 1 to 7, in which the enteric envelope or coating is substantially free of benzimidazole derivative.
9. The formulation of claim 4, in which the pre-coating layer or isolating layer is substantially free of benzimidazole derivative.
10. The formulation of anyone of the claims 1 to 9, in which the core comprises at least a tabletting excipient selected among the group consisting of microcrystalline cellulose, cellulose derivatives, lactose, mannitol, mono or disaccharide, and mixtures thereof, on which at least one lipophilic antioxidant is attached.
11. The formulation of anyone of the preceding claims, in which at least one lipophilic antioxidant agent is selected from the group consisting of derivatives of vitamin E (α-tocopherol) and mixtures thereof.
12. The formulation of claim 12, in which the lipophilic antioxidant comprises at least vitamin E polyethylene glycol succinate (Vitamin E TPGS).
13. The formulation of claim 4, in which the pre-coating layer or the isolating layer comprises at least a polymer selected from the group consisting of povidone, derivatives of povidone, derivatives of cellulose, and mixtures thereof.
14. The formulation of anyone of the preceding claims, in which the enteric layer or envelope comprises at least one cellulosic polymer or cellulosic derivative.
15. The formulation of claim 14, in which the enteric layer or envelope comprises at least hypromellose phthalate.
16. The formulation of anyone of the claims 1 to 15, in which the enteric coating or envelope comprises at least an acrylic/methacrylic polymer or copolymer, preferably a methacrylic acid copolymer.
17. The formulation of anyone of the preceding claims, in which the benzimidazole derivative is omeprazole.
18. The formulation of anyone of the claims 1 to 16, in which the benzimidazole derivative is selected from the group consisting of benzimidazole derivatives inhibiting the proton pump, pantoprazole, lansoprazole, omeprazole and mixtures thereof.

19. The formulation of anyone of the preceding claims, in the form of a tablet or capsule containing from 5 to 80 mg omeprazole.

20. A process for the preparation of a formulation of anyone of the preceding claims, in which the core is prepared from a mixture comprising a tabletting excipient on which a lipophilic antioxidant is attached and a benzimidazole derivative, and in which the core is provided with at least an enteric layer or envelope.

21. The process of claim 19, in which the tabletting excipient on which a lipophilic antioxidant is attached is prepared by mixing the lipophilic antioxidant in molten phase with tabletting excipient.

22. The process of claim 19 or 20, in which the core is manufactured by direct compression.

23. The process of anyone of the claims 19 to 22, in which the core has the form of a tablet or granules, said tablet or granules being provided with an enteric coating or with a pre-coating by using the pan-coating technology or the fluid bed technology.

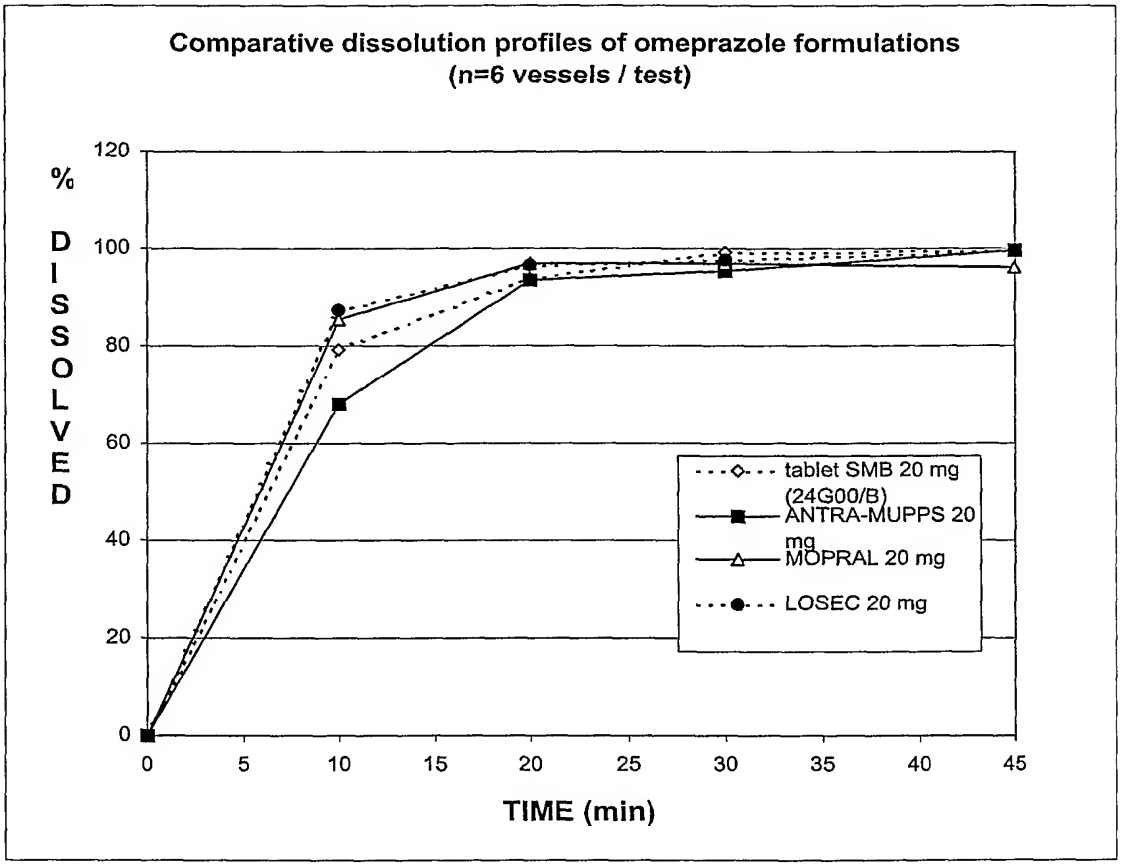
Comparative dissolution profiles of omeprazole formulations
(n=6 vessels / test)
% DISSOLVED
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
45
TIME (min)
tablet SMB 20 mg (24G00/B)
ANTRA-MUPPS 20 mg
MOPRAL 20 mg
LOSEC 20 mg

Figure 1

INTERNATIONAL SEARCH REPORT

onal Application No
PCT/BE 00/00126

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4439 A61K31/44 A61K9/28 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 32091 A (KAREHILL PER GUNNAR ;ASTRA AB (SE); LUNDBERG PER JOHAN (SE)) 1 July 1999 (1999-07-01)	1-4,8,9, 13-19
A	page 4, line 23 -page 5, line 11 page 5, line 26 -page 6, last line page 8, line 5 - last line page 9, line 25 page 14, line 14 - line 17 page 16, line 21 -page 18, line 20; claims 1-6,15; examples 5-7	20-23

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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Date of the actual completion of the international search	Date of mailing of the international search report
26 March 2001	03/04/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marttin, E

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

onal Application No
PCT/BE 00/00126

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 004 305 A (EISAI CO LTD) 31 May 2000 (2000-05-31)	1,2,4, 13-15, 17,18
A	page 2, paragraph 2 -page 3, paragraph 8 page 4, paragraph 15 - paragraph 16 page 5, paragraph 24 - paragraph 25 page 6, paragraph 32 page 6, paragraph 36 page 10, paragraph 58 - paragraph 60; examples 19-23	20-23
A	US 5 708 017 A (DAVE KAUSHIK J ET AL) 13 January 1998 (1998-01-13) column 1, line 46 - line 54 column 2, line 1 -column 3, line 56 column 4, line 12 - line 20 column 4, line 40 - line 58 claims 1,2; example 5	1-23
T	DE 199 18 434 A (BASF AG) 26 October 2000 (2000-10-26) column 1, line 1 - line 11 column 1, line 23 - line 41 column 1, line 66 -column 2, line 4 column 2, line 37 - last line column 3, line 62 - line 65; claims 1,4-7; examples 1,2,4	1-23

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ɔnal Application No
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